

One-day versus four-day antibiotic treatment for acute right colonic uncomplicated diverticulitis: A randomized clinical trial

Jung Ho Park , Hyoung Chul Park* , Bong Hwa Lee 

Department of Surgery, Hallym University College of Medicine, Anyang, Korea

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ABSTRACT

Background/Aims: Currently, right colonic uncomplicated diverticulitis is typically treated with antibiotic therapy. However, the optimal duration of treatment is unknown. The aim of the present study was to compare the treatment failure rates between 1- and 4-day antibiotic treatment protocols.

Materials and Methods: A prospective randomized study in adults presenting with uncomplicated diverticulitis at the first episode from July 2011 to June 2014 was performed. Patients were randomized to receive intravenous antibiotics for 1 day (1-day group) or intravenous and oral antibiotics for 4 days (4-day group). All patients received cefmetazole and metronidazole. Treatment failure was defined as readmission within 30 days and disease recurrence during the follow-up period.

Results: Overall, 87 and 89 patients were randomized to the 1-day and 4-day groups, respectively. All patients were successfully treated initially. The hospital length of stay was shorter in the 1-day group than in the 4-day group (3.1 vs. 3.8 days, respectively; $p < 0.001$). After discharge, there were no significant differences between the groups in treatment failure (15/87, 17.2% vs. 19/89, 21.3%; $p = 0.493$). In each group, there were readmission within 30 days (9.2% vs. 12.4%; $p = 0.502$) and recurrence over a median follow-up period of 32 months (10.3% vs. 9.0%; $p = 0.762$). In 34 patients who experienced treatment failure, 6 required surgery.

Conclusion: Single-day antibiotic treatment is as effective as 4-day therapy for the prevention of readmission and recurrence in patients with right colonic uncomplicated diverticulitis.

Keywords: Antibacterial agents, colonic, diverticulitis, treatment failure

INTRODUCTION

Right colonic diverticulitis has a high prevalence in Asian countries although complicated cases are relatively uncommon. Antibiotic use has been recommended for the treatment of acute colonic diverticulitis, and currently, the treatment of right colonic uncomplicated diverticulitis at the first episodes is typically managed conservatively with antibiotic therapy (1-3).

However, in clinical practice, medical treatment patterns vary widely (4). Prolonged antibiotic treatment increases medical costs. This indicates some benefits of limiting the use of long-term antibiotic therapy where possible.

Recent studies suggest that antibiotics may not play a critical role in the management of uncomplicated diverticulitis, particularly left-sided colonic disease (5,6). Previous studies also reported that the majority of patients with uncomplicated diverticulitis were not treated with antibiotics, indi-

cating that no antibiotic policy was acceptable. Furthermore, outpatient management without antibiotic therapy was feasible and resulted in low complication rates (7,8).

Right colonic diverticulitis has a lower complication rate than left-sided disease, and a recurrence can be successfully treated with conservative therapy (9). However, there is limited information about the safety of antibiotic reduction or omission in the management of right colonic uncomplicated diverticulitis. Thus, antibiotics are still frequently administered for extended periods in clinical practice.

Further, treatment guidelines, indicating the appropriate duration of antibiotic therapy and follow-up, have not yet been established.

In a previous study, diet restriction until the patient reported pain relief and antibiotic therapy for 4 days, including oral agents, were used (10). The majority of the

*Current Working in Center for Colorectal Cancer, National Cancer Center, Goyang, Korea

Corresponding Author: Hyoung Chul Park; greatpa1@ncc.re.kr

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patients experienced pain relief and exhibited normal blood test results within 1-2 days.

In this prospective trial, a 1-day antibiotic therapy protocol was compared with a 4-day regimen to evaluate the efficacy of short-term antibiotic treatment in patients with right colonic uncomplicated diverticulitis.

MATERIALS AND METHODS

Patients

A prospective randomized study in all patients aged >18 years who were admitted to the emergency room or outpatient clinics of our university medical center with suspected right colonic uncomplicated diverticulitis between July 2011 and June 2014 was performed. Patients were followed up from July 2011 to August 2017.

All eligible patients underwent abdominal computed tomography (CT) (Philips N.V, Amsterdam, Netherlands). Patients with right colonic uncomplicated diverticulitis confirmed by CT were included in the study.

Inflamed diverticulum, phlegmon formation (Hinchey Ia), and small (≤ 3 cm) pericolic abscess formation (partial Hinchey Ib) were considered to be consistent with the diagnosis of CT-based uncomplicated diverticulitis.

Exclusion criteria were an abscess >3 cm in diameter, Hinchey II diseases or worse, ongoing antibiotic therapy from other hospital, pregnancy, cephalosporin allergy, and refusal to provide consent.

Study design

Patients were randomized to receive intravenous antibiotics for 1 day (1-day group) or intravenous and oral antibiotics for 4 days (4-day group). Cefmetazole (2000 mg/day; SCD Pharmaceutical Co., Seoul, South Korea) and metronidazole (1500 mg/day; Daihan Pharmaceutical Co., Seoul, South Korea) were administered in both groups.

Patients received no oral nutrition (bowel rest) until their symptoms resolved, and then they resumed their regular diet. Blood tests, including white blood cell count and C-reactive protein level, were conducted on days 1 and 2 after presentation. Discharge criteria included the absence of pain and fever and an improvement in blood test results. No prophylactic treatment was provided after discharge. All patients were blinded to their treatment allocation.

The study endpoint was treatment failure defined as re-admission and disease recurrence during the follow-up period. Readmission was defined as recurrent pain with abnormal blood test results and radiological evidence of diverticulitis within 30 days after discharge. Recurrence was defined as the development of identical symptoms and radiological evidence of diverticulitis during the remaining follow-up period. Additionally, treatment failure risk factors in patients with right colonic uncomplicated diverticulitis were evaluated.

The study was approved by the appropriate Ethics Review Board of Hallym University and conducted in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines for randomized studies (11). Informed consent was obtained from all study participants. The study was registered with the Clinical Research Information Service (KCT0000125, <http://www.cris.nih.go.kr>).

Randomization

Patients were stratified into four cohorts by age (≤ 40 years and >40 years) and sex, and randomization was performed using a computer-generated program.

Within each cohort, the ratio of patients allocated to the 1-day and 4-day groups was 1:1. Sequentially numbered random codes (A, 1-day therapy and B, 4-day therapy) were used for each group.

For blinding purposes, identical preparations of normal saline with vitamins (Daihan Pharmaceutical Co.) were administered, and patients in the 1-day group received placebo in white paper wrapping identical to the packaging used for the antibiotic received by subjects in the 4-day group.

Follow-up and outcome

Patients were examined in the clinic twice within 30 days after discharge. Patients who were not readmitted within 30 days after treatment using medical chart review and telephone interviews 3 and 12 months after enrolment and again at the end of the study period in August 2017 were followed up. CT colonography or colonoscopic examinations were conducted on all patients at least once during the follow-up period.

The interpretation of readmission or recurrence was performed by two surgeons and radiologists based on clinical and laboratory findings and CT-verified diverticulitis. Clinical and laboratory findings were not considered to indicate readmission or recurrence without radiological evidence of disease.

Statistical analysis

Data were analyzed using Statistical Package for Social Sciences 14.0 software (SPSS, Inc.; Chicago, IL, USA). The sample size was calculated from an estimated treatment failure rate of 20% after 4 days of antibiotic therapy. An increase in the failure rate in the 1-day group to a maximum of 35% was considered tolerable. The necessary sample size of each group was 87 patients, with $\alpha=0.1$ and a power of 70% and including a dropout rate of 4%. Comparisons between the two groups were performed using χ^2 and independent samples *t*-tests. A *p*-value <0.05 was considered statistically significant.

RESULTS

During the 3-year period, 185 patients with a first episode of symptomatic acute right colonic uncomplicated diverticulitis were enrolled.

Of the 185 patients, 9 met our exclusion criteria, leaving 176 trial participants (96 men; mean age \pm standard deviation, 41.1 \pm 11.2 years; age range, 18–73 years). After randomization, 87 and 89 patients were randomized to the 1-day and 4-day groups, respectively. In the 4-day group, 32 patients completed the 4-day antibiotic therapy including 1 day of oral antibiotics (Figure 1). No patients in either group exhibited clinical deterioration or persistent-

ly abnormal blood test results during their hospitalization. The median follow-up period in all patients was 32 (1-53) months, including those with readmission or recurrence.

Clinical characteristics

There were no differences between the two groups in clinical or laboratory features. The length of hospital stay was shorter in the 1-day group than in the 4-day group (3.1 \pm 1.3 days vs. 3.8 \pm 1.2; *p* <0.001).

Six patients had a comorbid illness (3 diabetes, 1 liver cirrhosis, 1 renal disease, and 1 coronary artery disease). No additional therapy related to comorbidities was provided. There were no immunocompromized patients.

Pericolic abscess formation and multiple diverticula in 12 and 34 patients in the 1-day group, respectively, were suspected based on radiological findings. In the 4-day group, pericolic abscess in 18 patients and multiple diverticula in 35 patients were suspected (Table 1).

Analysis of treatment failure

Eight (9.2%) patients in the 1-day group and 11 (12.4%) patients in the 4-day group were readmitted within 30 days after discharge with recurrent pain due to CT-proven persistent diverticulitis.

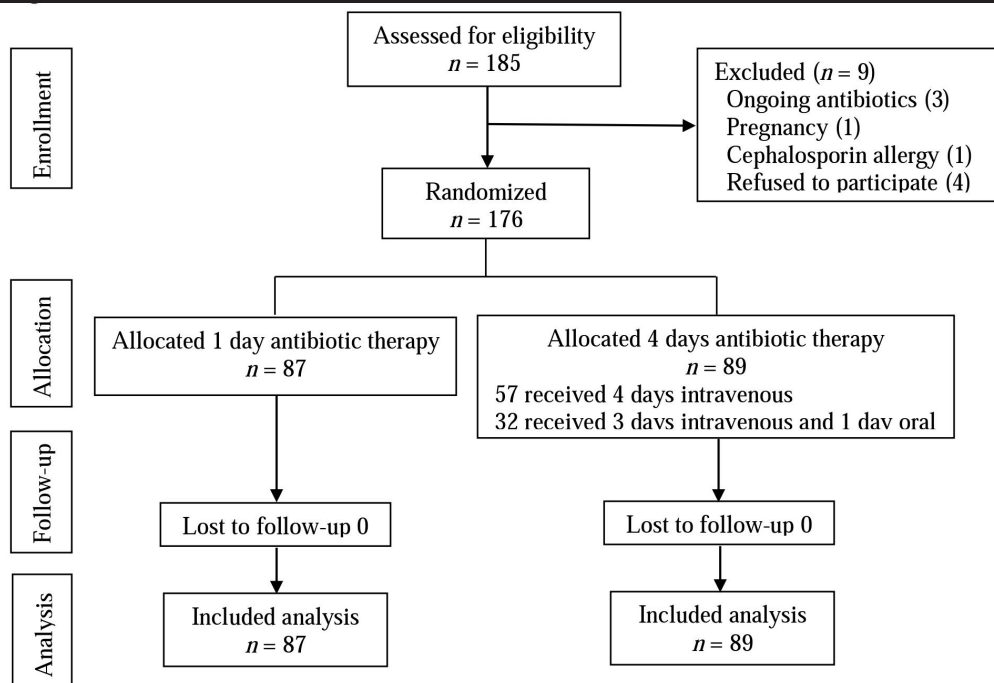


Figure 1. The CONSORT diagram for the trial.

Table 1. Characteristics and clinical outcomes in patients receiving 1 or 4 days of antibiotic treatment.

Variable	1-day group (n=87)	4-day group (n=89)	p
Age (years)	42.0±11.1	40.2±11.2	0.309*
Male/female	47/40	49/40	0.891**
BMI (kg/m ²)	22.9±3.1	23.0±2.9	0.754*
WBC count (10 ³ /μL)	11.2±3.2	11.1±3.1	0.875*
WBC count at 2 days (10 ³ /μL)	6.5±2.4	6.5±2.3	0.929*
CRP (mg/dL)	44.8±41.7	55.0±47.4	0.131*
CRP at 2 days (mg/dL)	22.7±31.5	21.9±28.1	0.864*
Body temperature (°C)	37.3±1.1	37.6±0.9	0.111*
Hospital stay (days)	3.4±1.3	3.8±1.2	0.041*
Pericolic abscess	12 (13.8%)	18 (20.2%)	0.259**
Multiple diverticula	34 (39.1%)	35 (39.3%)	0.974**
Location			0.605**
—Cecum	29 (33.3%)	33 (37.1%)	
—Ascending to transverse	58 (66.7%)	56 (62.9%)	
Diverticulitis location			0.847**
—Intraperitoneal	55 (63.2%)	55 (61.8%)	
—Retroperitoneal	32 (36.8%)	34 (38.2%)	

Values are expressed as mean±standard deviation or number (%).

*p calculated by the independent t-test.

**p calculated by the chi-square test.

BMI: body mass index; WBC: white blood cell; CRP: C-reactive protein.

There was no significant difference in the readmission rate between the two groups ($p=0.502$). Ten of the readmitted patients were discharged without further treatment after physical examination and improvement in their laboratory test results. The remaining patients received additional antibiotic therapy. Of these patients, three (one in the 1-day group and two in the 4-day group) underwent surgery for complicated diverticulitis.

Nine (10.3%) patients of the 1-day group and 8 (9%) patients of the 4-day group exhibited disease recurrence during the follow-up period. There was no significant difference in recurrence between the groups ($p=0.762$).

All patients in the 1-day group with disease recurrence received antibiotic therapy initially. Two of these patients underwent laparoscopic ileocolic resection for complicated diverticulitis. The remaining patients were successfully treated with additional antibiotic therapy.

Table 2. Characteristics and clinical outcomes in patients receiving 1 or 4 days of antibiotic treatment.

Variable	1-day group (n=87)	4-day group (n=89)	p*
Total treatment failure rate	15 (17.2%)	19 (21.3%)	0.493
Readmission within 1 month	8	11	0.502
Recurrence	9**	8	0.762
Treatment for failure			0.758
—Surgery	3	3	
—Conservative	14	16	

Values are expressed as number (%).

*p calculated by the chi-square test.

**Two patients experienced both readmission and recurrence.

All patients in the 4-day group with disease recurrence were treated with antibiotic therapy initially. One underwent laparoscopic ileocolic resection for peritonitis. The remaining patients were successfully treated with conservative management.

After the follow-up period, there was no statistically significant difference in the total treatment failure rate between the two groups (17/87, 19.5% vs. 19/89, 21.3%; $p=0.493$) (Table 2).

Risk factor of treatment failure

In our logistic regression analysis, only multiple diverticula were associated with treatment failure (hazard ratio (HR) 2.25, 95% confidence interval (CI) 1.01-4.99; $p=0.046$). Intraperitoneal diverticulitis may be related to treatment failure, but this tendency was not statistically significant (HR 2.32, 95% CI 0.96-5.6; $p=0.063$). Other clinical and laboratory characteristics, including body mass index or smoking history, showed no significant relationship with treatment failure.

DISCUSSION

This randomized clinical trial of patients with CT-verified acute right colonic uncomplicated diverticulitis demonstrated that readmission and disease recurrence rates were similar in patients receiving 1 or 4 days of antibiotics. Based on our results, we postulate that long-term antibiotic therapy does not effectively stimulate recovery or prevent recurrence. The 1-day antibiotic protocol shortened hospital stay and could decrease medical costs in patients with right colonic diverticulitis. Additionally, a regimen of cefmetazole and metronidazole is adequate treatment in this population.

According to previous studies, patients with diverticulitis typically receive antibiotics for 5-7 days (12-14).

However, recent guidelines for the management of acute left colonic uncomplicated diverticulitis indicate that antibiotics should not be used routinely. Additionally, long-term antibiotic treatment did not reduce the diverticulitis recurrence rate.

Most first episodes of uncomplicated diverticulitis appear to involve mucosal inflammation alone and can be controlled by anti-inflammatory drugs. Therefore, it is likely that infection sources do not play a prominent role in these cases. Antibiotics could be used, at the very least, to prevent bacterial infection.

In the present study, few patients with recurrent diverticulitis required bowel surgery. Choi et al. (15) demonstrated a higher mortality rate in Asian patients and right-sided diverticulitis. The optimal management of right colonic diverticulitis has been difficult to determine in Western populations as it is rare and difficult to diagnose in these patients.

In the present study, only six patients underwent surgery for suspected complicated diverticulitis, and the majority received additional antibiotic therapy.

In a previous study, we reported that multiple diverticula and intraperitoneal diverticulitis were risk factors for recurrence in patients with right-sided colonic diverticulitis (16). In this study, 19/69 (27.5%) patients with multiple diverticula experienced treatment failure. On the other hand, in our patients with intraperitoneal diverticulitis, 26/110 (23.6%) experienced treatment failure. In patients with both risk factors, treatment failure occurred in 14/43 (32.6%).

Our study has limitations. Our investigation did not include a no antibiotic therapy group, which is an important limitation. However, we designed the study before there was evidence supporting the non-use of antibiotics. The current trial demonstrated that limiting the duration of antibiotic treatment in patients with right colonic diverticulitis is safe. Thus, it is now possible to perform a prospective trial evaluating a no antibiotic protocol in this population.

In conclusion, although there is no consensus regarding right colonic uncomplicated diverticulitis treatment guidelines, the findings of the present study indicate that

1-day antibiotic therapy is as effective as 4 days of conventional treatment in preventing readmission and disease recurrence.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Hallym University.

Informed Consent: Written informed consent was obtained from the patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - J.H.P., H.C.P., B.H.L.; Design - J.H.P., H.C.P., B.H.L.; Supervision - H.C.P., B.H.L.; Data Collection and/or Processing - J.H.P., H.C.P.; Analysis and/or Interpretation - J.H.P., H.C.P., B.H.L.; Literature Search - J.H.P., H.C.P.; Writing Manuscript - J.H.P., H.C.P.; Critical Review - B.H.L.

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